

Iron-polyphenol complexes in cancer theranostics: Coordination chemistry, therapeutic mechanisms, and molecular imaging

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ARTICLE INFO

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Article history

Received 12 July 2026

Accepted as revised 2 September 2026

Available online 14 September 2026

Keywords

Iron-polyphenol complexes, metal-phenolic networks, cancer nanotheranostics, immunomodulation, magnetic resonance imaging, good manufacturing practice (GMP).

ABSTRACT

Background: Iron-polyphenol complexes have emerged as promising theranostic platforms by integrating the biological activity of polyphenols with the redox and coordination properties of iron. Their ability to form discrete molecular complexes and metal-phenolic networks (MPNs) provides tunable control over iron stability, redox activity, cargo delivery, and imaging performance. Since cancer cells exhibit altered iron metabolism and increased dependence on iron availability, these systems offer opportunities for exploiting tumor-specific vulnerabilities through ferroptosis, chemodynamic therapy, and multifunctional molecular imaging.

Objectives: This review aims to summarize recent advances in iron-polyphenol systems for cancer theranostics, focusing on the relationship between coordination chemistry, therapeutic mechanisms, and imaging applications. Particular emphasis is placed on discrete Fe-polyphenol complexes, metal-phenolic networks, coordination polymers, and iron-containing hybrid nanoplateforms, including their structural characteristics, anticancer mechanisms, imaging capabilities, biological limitations, and translational challenges.

Materials and methods: A structured literature search was conducted using PubMed, Scopus, and Web of Science from database inception to August 2026. Studies related to Fe(II)/Fe(III)-polyphenol coordination systems, including polyphenolic ligands such as catechol, tannic acid, gallic acid, quercetin, and related architectures, were evaluated. Eligible studies included original research investigating coordination chemistry, cancer therapy, molecular imaging, biodistribution, pharmacokinetics, safety, or translational aspects. Non-iron metal-polyphenol systems, iron materials lacking polyphenolic coordination, and unrelated applications were excluded.

Results: Iron-polyphenol platforms demonstrate diverse anticancer activities through coordination-controlled mechanisms, including ferroptosis induction, Fe-mediated chemodynamic therapy, photothermal therapy, drug delivery, and immune modulation. The therapeutic and imaging behavior of these systems is strongly influenced by ligand identity, Fe oxidation state, coordination stoichiometry, pH responsiveness, and supramolecular architecture. Iron-polyphenol complexes and MPNs also show potential as gadolinium-free MRI contrast agents, photoacoustic imaging platforms, and immune-cell tracking probes. However, clinical translation remains limited by structural heterogeneity, biological barriers such as protein corona formation and reticuloendothelial system uptake, incomplete biodistribution understanding, long-term iron toxicity concerns, and challenges in scalable manufacturing and quality control.

Conclusion: Iron-polyphenol complexes represent a versatile class of theranostic materials that bridge natural product chemistry, redox-regulated cancer therapy, and molecular imaging. Their tunable coordination chemistry enables rational development of multifunctional platforms; however, successful clinical translation requires improved structural standardization, reproducible manufacturing, comprehensive safety evaluation, and quality-controlled production strategies. Continued investigation into coordination-structure-function relationships will be essential for advancing iron-polyphenol systems toward clinically relevant precision cancer theranostics.

Introduction

Importance of metal-polyphenol interactions

Transition metals such as Fe, Cu, Co, Mn, Ni, and Zn are vital for biological activities, acting as enzyme cofactors and structural elements that promote catalysis, redox control, and cellular signaling.¹⁻³ Because their coordination chemistry facilitates electron-transfer reactions essential to metabolism and oxidative processes, redox-active ions especially Fe(II/III) and Cu(I/II) are prominent in biological contexts.^{2,4} With more than 8,000 structures, polyphenols are a broad class of secondary metabolites found in plants that include phenolic acids, flavonoids, tannins, stilbenes, and lignans.⁵ Their aromatic rings bearing hydroxyl substituents allow them to 1) donate hydrogen atoms or electrons to neutralize radicals, and 2) delocalize unpaired electrons through π -conjugation, underpinning their antioxidant activity.^{6,7} Metal-polyphenol coordination occurs through binding of transition metals to catechol, galloyl, or carbonyl-hydroxyl groups, altering polyphenol

redox properties and radical-scavenging activity.^{6,8} In many cases, complexation with high-charge-density metals such as Fe(III) can enhance electron delocalization and strengthen antioxidant responses, whereas other metals may distort the electron distribution or introduce competing redox pathways that diminish protective activity.^{6,8,9} Metal-phenolic networks (MPNs), dynamic supramolecular coatings, and capsules built in mild aqueous conditions are made possible by multivalent coordination between metal ions and polyphenols, which goes beyond discrete complexes.¹⁰⁻¹² MPNs are attractive in nanomedicine because they can be deposited on diverse templates, exhibit pH-responsive coordination, and provide tunable permeability, stability, and cargo loading.¹⁰⁻¹³ Consequently, controlled metal-polyphenol interactions provide a rational strategy to design multifunctional systems spanning antioxidant regulation, antimicrobial activity, drug delivery, catalysis, and bioimaging.⁹⁻¹³

Iron role and cancer transition

Iron is essential for oxygen transport, mitochondrial metabolism, DNA synthesis, and redox-regulated cellular processes. Transferrin-mediated transport, ferritin storage, ferroportin-dependent export, and hepcidin regulation all closely regulate systemic iron availability, preserving a balance between the toxicity of excess labile iron and physiological iron requirements. In cancer, however, this balance is frequently reprogrammed to support rapid proliferation and metabolic activity. Tumor cells commonly increase iron acquisition and retention through altered expression of iron-handling proteins, including increased transferrin receptor-mediated uptake and reduced ferroportin-dependent export, resulting in expansion of intracellular iron pools. This iron dependence simultaneously creates a therapeutic vulnerability because redox-active Fe(II) can catalyze Fenton chemistry, lipid peroxidation, and ferroptosis. These tumor-specific alterations provide a strong biological rationale for engineering iron-polyphenol complexes and metal-phenolic networks as controlled iron-delivery, redox-modulating, and theranostic platforms.^{14,15}

Scope and novelty of iron-polyphenol systems in cancer theranostics

Recent reviews have broadly examined metal-phenolic networks across multiple metal ions or surveyed metal-polyphenol coordination polymers. However, this review specifically addresses iron-polyphenol systems and integrates three interconnected levels that are often discussed separately: molecular Fe-polyphenol coordination and speciation, redox-dependent anticancer mechanisms like ferroptosis, chemodynamic, and photothermal therapies, and molecular-imaging applications like T1-weighted MRI and immune-cell tracking. Both discrete molecular Fe-polyphenol complexes and extended coordination architectures are critically examined for structural reproducibility, biological destiny, safety, and translational restrictions.

In this review, iron-polyphenol systems are defined as materials in which Fe(II) and/or Fe(III) directly participate in coordination with polyphenolic, catechol, galloyl, or related oxygen-donor ligands. The scope encompasses discrete molecular Fe-polyphenol complexes, metal-phenolic networks (MPNs), Metal-organic frameworks (MOFs) and nanoscale coordination polymers (NCPs) in which iron-polyphenol coordination constitutes a functional component of the architecture. Hybrid nanoplateforms are included when the Fe-polyphenol coordination unit contributes directly to drug delivery, redox activity, imaging, or therapeutic performance.

Materials and methods

A structured literature search was performed in PubMed, Scopus, and Web of Science from 1999 to

2026. Search strategies were adapted to each database and combined terms relating to iron and iron oxidation states ('iron', 'Fe(II)', 'Fe(III)'), polyphenolic ligands and architectures ('polyphenol', 'catechol', 'galloyl', 'tannic acid', 'gallic acid', 'quercetin', 'metal-phenolic network', 'coordination polymer'), therapeutic mechanisms ('cancer', 'tumor', 'ferroptosis', 'chemodynamic therapy', 'photothermal therapy', 'drug delivery', 'immunotherapy'), and diagnostic applications ('MRI', 'magnetic resonance imaging', 'molecular imaging', 'photoacoustic imaging', 'theranostic'). Reference lists of relevant articles were additionally examined to identify foundational studies. English-language original studies on Fe(II)/Fe(III)-polyphenol coordination, physicochemical properties, cancer-related therapeutic mechanisms, molecular imaging, pharmacokinetics, biodistribution, safety, or translational considerations were eligible. For background and primary study identification, relevant reviews were used. Exclusively non-iron metal-polyphenol systems, iron formulations without a polyphenolic coordination component, non-biomedical applications without mechanistic relevance, conference abstracts without full reports, duplicate publications, or non-English reports were excluded. Seminal investigations were kept to build fundamental coordination chemistry. Records were screened by title and abstract, then full-text, according to eligibility criteria. There was no quantitative evidence synthesis or risk-of-bias evaluation because this was a structured narrative review.

Data analysis

The selected literature was qualitatively examined and classified depending on the kind of iron-polyphenol system, which included discrete coordination complexes, metal-phenolic networks, coordination polymers, and iron-based nanoplateforms. The investigations were evaluated according to their coordination properties, iron oxidation state, ligand structure, therapeutic mechanisms, imaging applications, biological models, and known limitations. The link between coordination chemistry and functional results was studied in detail, including ferroptosis induction, chemodynamic therapy, photothermal impacts, and MRI performance. A comparative investigation was conducted to identify existing issues in stability, repeatability, biodistribution, toxicity, and clinical translation.

Results

Literature selection and review scope

A comprehensive literature search was performed using PubMed, Scopus, and Web of Science databases to identify studies related to iron-polyphenol coordination systems, cancer theranostics, therapeutic mechanisms, and molecular imaging applications. Approximately 150 articles were initially screened based on title, abstract, and full-text assessment. After applying predefined inclusion and exclusion criteria, 65 articles were selected for detailed analysis in this review.

The selected studies were categorized according to iron-polyphenol system type, including discrete coordination complexes, metal-phenolic networks, coordination polymers, and iron-based imaging or therapeutic platforms. The findings from these studies are discussed in the following sections, focusing on coordination chemistry, anticancer mechanisms, imaging applications, biological challenges, and future translational perspectives.

Coordination chemistry of iron-polyphenol complexes Iron-polyphenol interactions

Polyphenols are natural iron chelators that regulate iron homeostasis and oxidative stress through strong Fe(II)/Fe(III) binding, contributing to their antioxidant and therapeutic effects.^{6-8,16} At the molecular level, polyphenols regulate iron chemistry through metal chelation and redox modulation. By sequestering labile iron, they limit Fe(II)-mediated Fenton reactions, reducing hydroxyl radical generation and protecting biomolecules from oxidative damage.^{6,7,17} Depending on ligand structure and redox environment, some polyphenols can participate in iron redox cycling, either stabilizing

Fe(III) in redox-inactive complexes or reducing Fe(III) to Fe(II), thereby shifting the balance between antioxidant and pro-oxidant behavior.⁶⁻⁸ Iron-polyphenol interactions are context dependent, reducing oxidative stress under normal conditions but potentially promoting localized redox activity in acidic or oxidative environments.¹⁸⁻²⁰

Polyphenol specific coordination of iron

Polyphenols containing catechol or galloyl groups act as oxygen-donor ligands that strongly chelate Fe³⁺, forming stable iron-phenolate complexes. Fe³⁺ typically exhibits octahedral coordination, generating mono-, bis-, or tris-complexes as characteristic iron-polyphenol binding motifs.^{18,20,21} Fe-polyphenol coordination is multivalent, reversible, and strongly pH-dependent (Figure 1). The protonation state of phenolic groups governs binding strength and complex stability, with higher pH favoring ligand bridging and supramolecular assembly.¹⁸⁻²⁰ A key feature of Fe-polyphenol complexes is the coupling of iron binding with redox activity. Polyphenol ligands can facilitate Fe³⁺/Fe²⁺ interconversion, contributing to the characteristic antioxidant and pro-oxidant behavior of these systems.^{21,22}

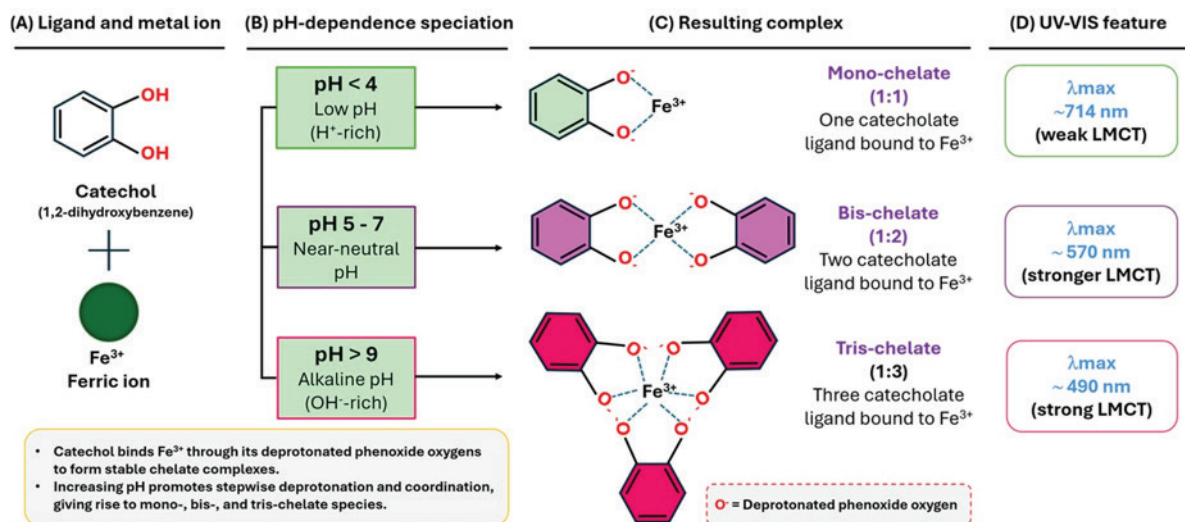


Figure 1. Iron catechol complexes at varying pH. Adapted from Bijlsma et al. (2020), Scientific Reports, 10, 8288, under the Creative Commons Attribution 4.0 International License (CC BY 4.0). Changes were made to the layout and annotations.²³

Metal-phenolic network formation

The multidentate nature of polyphenols enables the assembly of iron-polyphenol complexes into metal-phenolic networks (MPNs), where Fe³⁺ ions act as dynamic crosslinkers between polyphenol units, forming extended supramolecular structure.^{10-12,24} MPNs form rapidly through Fe-polyphenol coordination and retain the pH-dependent, reversible binding characteristics of discrete complexes. Their supra-molecular structure confers additional properties, including stimuli-responsive disassembly, tunable permeability, and adaptive redox behavior.^{11, 25}

Chemical basis of iron-polyphenol coordination

Fe(III) easily chelates polyphenols with galloyl or catechol groups, creating stable octahedral complexes that constitute the foundation for metal-phenolic networks (MPNs) and discrete iron-polyphenol complexes. The degree of hydroxylation, ligand structure, and pH of the surrounding environment all affect the stability and coordination behavior of these complexes.^{18, 20, 21}

Spectroscopic signatures of complex formation

Ligand-to-metal charge-transfer (LMCT) bands in the UV-visible spectrum result from phenolate oxygen

atoms donating electrons to Fe(III) centers in iron-polyphenol complexes (Figure 2,3).²⁶ The position and intensity of these bands vary systematically with coordination stoichiometry, ligand identity, and pH,

enabling discrimination between mono-, bis-, and tris-chelate species. Complementary FTIR and EPR analyses further confirm metal coordination, oxidation state, and ligand field symmetry.^{27, 28}

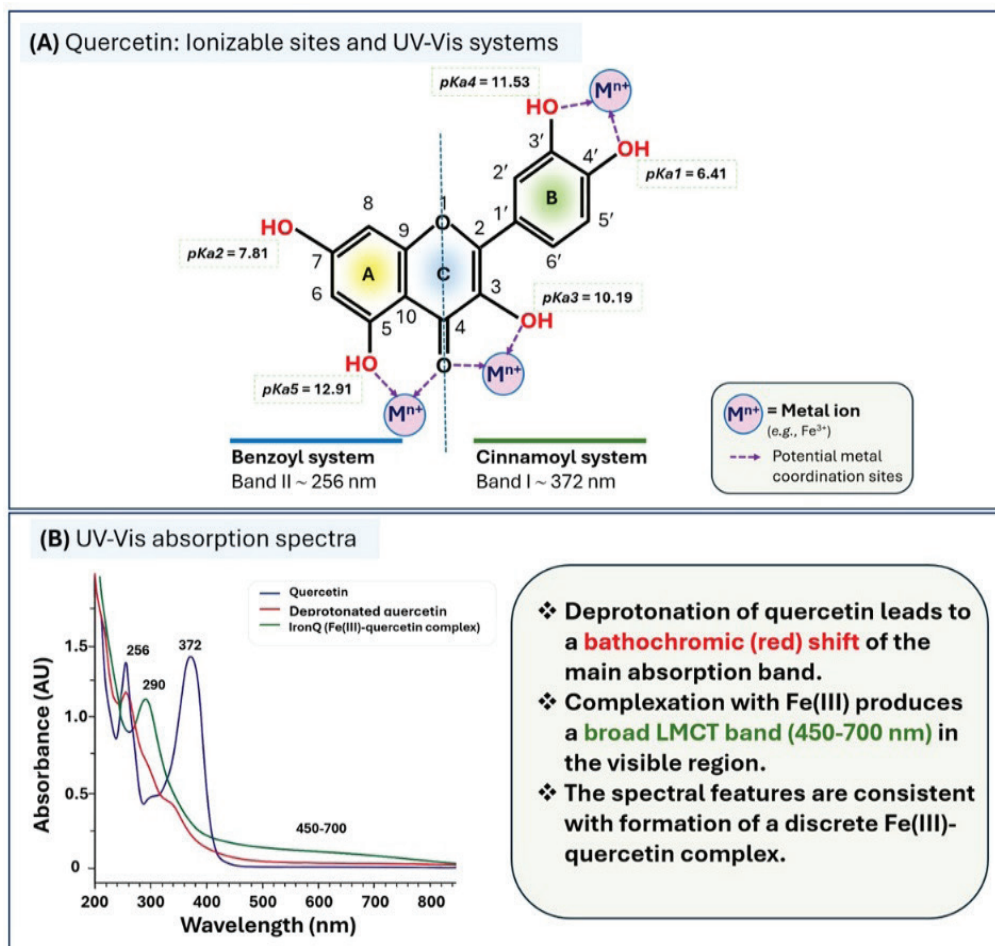


Figure 2. Proposed quercetin metal-binding sites (A) and UV-Vis spectral shifts upon Fe(III) coordination (B), evidencing the formation of Fe(III)-quercetin complexes. Adapted from Papan et al. (2020), Contrast Media and Molecular Imaging, Article 8877862, under the Creative Commons Attribution License. Changes were made to the layout and annotations.²⁷

Coordination-structure-function relationships

Coordination chemistry is not simply a structural feature of iron-polyphenol systems but a central determinant of their therapeutic and imaging behavior. Protonation of phenolic oxygen donors at lower pH can weaken Fe-O coordination and promote conversion from higher-order coordination states toward lower-order complexes or network disassembly, facilitating iron and cargo release in acidic biological compartments.^{6,11,20} In redox-active formulations, released or accessible Fe(III) may undergo reduction to Fe(II), increasing the availability of Fenton-active iron and thereby promoting hydroxyl-radical generation, lipid peroxidation, chemodynamic therapy, and ferroptosis. Conversely, stronger multivalent coordination may improve extracellular stability but reduce immediate iron accessibility,

illustrating the need to balance circulation stability with intracellular activation. Fe-polyphenol coordination also generates ligand-to-metal charge-transfer absorption, linking coordination state and ligand structure to photothermal behavior.²⁹⁻³¹ For MRI, the coordination environment influences accessibility and exchange of water protons around paramagnetic Fe centers consequently, relaxivity depends not only on total iron concentration but also on ligand architecture, hydration, molecular dynamics, and measurement conditions. Thus, ligand identity, Fe oxidation state, coordination stoichiometry, pH responsiveness and supramolecular architecture collectively determine the balance between stability, therapeutic activation and imaging performance.^{27, 32}

Therapeutic applications of iron-polyphenol complexes

The biological significance of polyphenols is closely associated with their ability to chelate iron. Iron-polyphenol complexation regulates iron availability, enhances antioxidant capacity, suppresses iron-mediated oxidative damage, and contributes to the maintenance of cellular redox homeostasis. Through these mechanisms, iron-polyphenol complexes have attracted considerable interest as therapeutic agents for preventing and treating diseases associated with oxidative stress and iron dysregulation.^{16,28} Beyond their antioxidant functions, iron-

polyphenol complexes possess unique physicochemical characteristics, including tunable coordination chemistry, redox activity, and structural adaptability, which enable the rational design of multifunctional biomedical platforms. Depending on the ligand structure and coordination architecture, these systems range from discrete molecular complexes, such as iron-flavonoid complexes, to supramolecular metal-phenolic networks (MPNs), providing a versatile foundation for applications in cancer therapy, molecular imaging, drug delivery, and immunomodulation (Table 1).¹⁰

Table 1. Representative polyphenols and catechol-containing compounds that coordinate Fe(II) and/or Fe(III).

Ligand/system	Fe state	Binding motif	Coordination characteristics	Biomedical relevance	Reference
Catechol	Fe(III)	Catecholate oxygen donors	Mono-, bis-, tris-chelation strong pH dependence LMCT transitions	Model system for Fe redox chemistry	7
Protocatechuic acid (PCA)	Fe(III)	Catechol + carboxylate	Stable Fe-phenolate complexes; pH-dependent speciation	Iron-polyphenol chemistry and MRI contrast research	6
Gallic acid (GA)	Fe(II)/Fe(III)	Galloyl groups	1:1-1:3 complexes possible supramolecular assembly	Fe-GA nanoparticles, imaging and therapy	33
Quercetin	Fe(II)/Fe(III)	3',4'-catechol and 3-OH/4-keto sites	Discrete complexes site- and pH-dependent coordination	IronQ MRI tracking and immunomodulation	27,34
EGCG	Fe(II)/Fe(III)	Gallate and catechol groups	Fe binding with antioxidant/redox regulation	Iron regulation and biological activity studies	35
Tannic acid	Fe(II)/Fe(III)	Multidentate galloyl groups	Dynamic Fe-TA networks; reversible coordination MPN formation	Drug delivery, photothermal therapy, MRI theranostics	11,12
Ellagic acid	Fe(III)	Polyphenolic lactone groups	Fe coordination polymer formation possible	MRI/photoacoustic imaging platforms	36

Anticancer mechanisms

Iron-polyphenol anticancer systems include discrete Fe-polyphenol complexes (e.g., Fe-quercetin) and metal-phenolic networks (Table 2). While MPNs are widely used in nanomedicine, discrete complexes such as IronQ remain important due to their stable coordination, redox activity, biocompatibility, and potential for both

therapy and imaging.^{27, 34} Iron coordination enhances quercetin stability and anticancer activity. Likewise, iron-polyphenol MPNs such as Fe-TA and Fe-GA promote chemotherapy, ferroptosis, photothermal, and chemodynamic therapies by increasing iron availability and ROS generation, thereby disrupting tumor redox balance and overcoming drug resistance.^{37,38}

Table 2. Summary of iron-polyphenolic complexes and their anticancer mechanisms.

System	Composition	Material class	Main mechanism / function	Cancer model	Evidence level	Reference
Fe(III)-TA MITA (Metal-Ion/Tannic Acid Assembly)	Fe(III)+ tannic acid	Metal-phenolic assembly	NIR photothermal conversion; multimodal imaging (photothermal imaging, photoacoustic imaging and MRI)	Tumor models (in vitro and in vivo)	Preclinical	39
Fe-TA MPN nanoparticles	Fe(III)+ tannic acid	Metal-phenolic network nanoparticle	Fe(III)/Fe(II) redox cycling, Fenton chemistry, ferroptosis induction, chemotherapy and photothermal therapy synergy	Oral squamous cell carcinoma	<i>In vitro</i> + <i>in vivo</i>	38
Fe-GA coordination polymer nanoparticles	Fe(III)+ gallic acid	Iron-gallic acid coordination polymer nanoparticles	ROS generation, photothermal therapy, multimodal MRI/ photoacoustic imaging	Tumor-bearing models	<i>In vitro</i> + <i>in vivo</i>	40
IronQ	Fe(III)+ quercetin	Discrete iron-polyphenol complex	T1-weighted MRI contrast and biological cell tracking	Cell tracking/ preclinical models	<i>In vitro</i> and pre-clinical	34
Iron(III)-tannic molecular nanoparticles	Fe(III)+ tannic acid	Molecular nanoparticle	Enhanced autophagy effect and T1 MRI contrast enhancement	Liver cell lines	<i>In vitro</i>	41

Ferroptosis

Iron-polyphenol compounds can cause ferroptosis, which is an iron-dependent cell death mechanism triggered by lipid peroxidation. These systems encourage ferroptosis by increasing intracellular iron levels, boosting Fenton reactions, and reducing antioxidant defenses. Fe-based MPNs allow for regulated iron release in the tumor microenvironment, which increases oxidative stress and overcomes multidrug resistance.^{42, 43}

Chemodynamic therapy

Chemodynamic therapy (CDT) utilizes Fe(II)-mediated Fenton reactions to generate cytotoxic ROS. Iron-polyphenol complexes enhance CDT through targeted iron delivery, promotion of Fe(III)/Fe(II) redox cycling, and tumor microenvironment-responsive iron release. Advanced systems incorporating peroxide-generating components further amplify ROS production, improving therapeutic efficacy while minimizing off-target toxicity.^{28, 44, 45}

Photothermal therapy

Iron-polyphenol assemblies, particularly Fe(III)-tannic acid MPNs, exhibit strong NIR absorption and efficient photothermal conversion, enabling effective tumor ablation. Under NIR irradiation, Fe-TA nanoparticles rapidly generate cytotoxic heat and synergistically enhance ferroptosis and chemodynamic therapy by accelerating redox reactions and lipid peroxidation.⁴⁴⁻⁴⁶

Immunomodulation

Iron-polyphenol complexes enhance antitumor immunity by inducing immunogenic cell death via ferroptosis and related therapies, leading to dendritic cell activation within the tumor microenvironment.⁴⁷ Iron-polyphenol MPNs can modulate immune checkpoint signaling, suppress immune evasion, and enhance T-cell-mediated antitumor responses.⁴⁸ IronQ promotes M2-to-M1 macrophage repolarization via ROS-mediated signaling, enhancing antitumor immune responses.³⁴

Diagnostic applications of iron-polyphenol complexes
Magnetic resonance imaging (MRI)

The longitudinal relaxivity (r_1) of iron-polyphenol complexes depends mainly on coordination geometry, ligand exchange kinetics, and water accessibility at the Fe(III) center rather than iron content alone. Catechol- and galloyl-containing ligands create labile coordination environments that facilitate water interactions and enhance T_1 relaxation (Table 3).⁴⁹ Fe(III)-tannic acid (Fe-TA) assemblies function as T_1 MRI contrast agents, exhibiting pH-dependent relaxivity and enhanced signal intensity in tumor models. Systems such as Fe-TA further improve stability, biocompatibility, and T_1 -dominant contrast, with performance approaching that of gadolinium-based agents. Ligand engineering, including ellagic acid-Fe and Fe-gallic acid coordination

polymers, enables multimodal imaging capabilities such as photoacoustic imaging and PET/MR, highlighting

the versatility of iron-polyphenol platforms for diagnostic applications.⁵⁰⁻⁵²

Table 3. Iron-polyphenol MRI platforms and their biological properties.

System	Composition	MRI conditions	Relaxivity information	Imaging role	References
Fe3+-P3-PVP dendritic complex	Fe(III)-polyphenol dendritic complex	0.5-3 T	Reported r1 around 3.34 mM ⁻¹ s ⁻¹ relaxivity field dependent	T1-weighted MRI contrast	53
Fe-TA MPNs	Fe(III)-tannic acid network	Study-specific phantom/cellular conditions	Reported r1 around 3.08 mM ⁻¹ s ⁻¹	T1-MRI and theranostic applications	41
Fe-GA coordination polymer nanoparticles	Fe(III)-gallic acid CPNs	Study-specific MRI conditions	Relaxivity reported in original study compare only under matched conditions	MRI/photoacoustic imaging	40
Ellagic acid-Fe NCPs	Fe(III)-ellagic acid coordination polymer	1.5 T	r1 approximately 2.54 mM ⁻¹ s ⁻¹	T1-MRI + photoacoustic imaging	36
Gd-DTPA (Magnevist benchmark)	Gadolinium chelate	1.5 T	Clinical comparison benchmark only	Reference contrast agent	54

Immuno-MRI and immune cell tracking

Immuno-MRI enables noninvasive visualization of immune cells within the tumor microenvironment. Iron-polyphenol complexes are particularly attractive probes because they combine MRI contrast with immunomodulatory activity. Iron(III)-quercetin (IronQ) accumulates in macrophages, enhances T₁-weighted MRI signals, and promotes M2-to-M1 macrophage repolarization through ROS-mediated ERK/NF- κ B signaling. The associated MRI signal changes correlate with immune activation, highlighting the potential of iron-polyphenol probes for monitoring tumor immune remodeling.^{27,34,55,56}

Discussion

Structural definition, reproducibility, and standardization

A major challenge for iron-polyphenol systems is their structural heterogeneity, as coordination behavior depends on factors such as pH, ligand composition, and redox conditions. Future research should focus on chemically defined and modular architectures with controlled size and composition to improve reproducibility, scalability, and clinical translation.^{11,55}

Biological barriers, bio distribution and in vivo stability

The transition of iron-polyphenol nanoplateforms from controlled experimental systems to systemic administration introduces additional biological barriers that remain insufficiently characterized. Following entry into the bloodstream, nanoparticle surfaces rapidly

interact with plasma proteins and other biomolecules, generating a biomolecular corona that can alter hydrodynamic size, surface charge, colloidal stability, cellular recognition, and targeting behavior. Opsonization may promote recognition by the mononuclear phagocyte or reticuloendothelial system, particularly Kupffer cells in the liver and macrophages in the spleen, thereby shortening circulation time and reducing the fraction of administered material reaching the tumor. This issue is particularly relevant to dynamically coordinated metal-phenolic assemblies because their physicochemical stability may depend strongly on pH, buffer composition, ligand-metal stoichiometry, and interactions with biological components. Although some engineered MPN nanoparticles retain colloidal stability in serum-containing media, such behavior is formulation-dependent and cannot be generalized across the entire class. Study demonstrated that assembly conditions can change nanoparticle sizes over approximately 50-270 nm and that some MPN formulations remained stable in medium containing 10% fetal bovine serum while degrading under acidic conditions. Future studies should therefore evaluate protein-corona formation, stability in whole serum or plasma, iron and polyphenol release kinetics, pharmacokinetics, and quantitative organ biodistribution under physiologically relevant conditions.⁵⁷⁻⁵⁹

Long term iron handling and systemic biosafety

Iron-polyphenol therapies that increase the

intracellular labile iron pool to boost Fenton chemistry or ferroptosis may have long-term biosafety issues. Degradation of an iron-containing nanoplatform releases iron into physiological storage, transport, and recycling pathways, but repeated dosage or insufficient clearance may disrupt systemic iron homeostasis. Other iron-containing nanomaterials show that particle size, coating, and surface chemistry strongly influence mononuclear phagocyte uptake, with liver and spleen accumulation and clearance lasting weeks to months. These findings highlight the necessity for platform-specific pharmacokinetic and toxicological study of iron-polyphenol complexes. Iron-driven lipid peroxidation can damage normal tissues and immune cells, including hepatic and renal tissues, and ferroptosis is not tumor-specific. Thus, long-term preclinical studies should include repeated-dose exposure, recovery periods, quantitative tissue iron measurements, serum ferritin and transferrin-related indices, hepatic and renal biochemical markers, histopathology, oxidative-stress markers, and urinary and fecal elimination to distinguish transient therapeutic iron redistribution from.⁶⁰⁻⁶²

Industrial scalability, reproducibility and quality control

Industrial translation of iron-polyphenol systems requires better raw material and coordination-driven assembly control. MPN formation is sensitive to metal-to-ligand ratio, pH, ionic strength, buffer composition, order and rate of mixing, reaction time, and temperature, while natural polyphenols vary in purity, oxidation state, hydration, and source-dependent composition. These variables affect coordination stoichiometry, particle size, polydispersity, surface charge, stability, and biological performance. Thus, pharmaceutical development should evolve from empirical formulation to Quality-by-Design, where a Quality Target Product Profile links important material, process, and quality aspects. For iron-polyphenol theranostics, release criteria may include ligand identity and purity, total and free iron content, Fe oxidation state and Fe:polyphenol stoichiometry, particle size and polydispersity, surface charge, morphology, spectroscopic coordination fingerprints, colloidal and serum stability, free ligand content, payload loading, iron-release kinetics, sterility/endotoxin limits, and functional assays like MRI relaxivity or Scalable manufacturing requires controlled and proven mixing methods and design-of-experiments approaches to establish process windows and show comparability between laboratory, pilot, and factory scales. GMP production will require stability-indicating analytical procedures, established release specifications, and batch-to-batch comparability.⁶³⁻⁶⁵

Limitations

Despite the considerable potential of iron-polyphenol systems for cancer therapy, several important limitations remain. Most published studies have been limited to in vitro experiments and small-animal models,

while comprehensive assessments of pharmacokinetics, biodistribution, long-term toxicity, and clinical safety remain restricted. The structural diversity of natural polyphenolic ligands and variations in coordination conditions also hinder reproducibility and direct comparisons across studies. Furthermore, differences in experimental protocols, such as MRI measurement conditions and biological evaluation methods, underscore the need for consistent characterization and reporting frameworks for clinical translation.

Conclusion

Iron-polyphenol complexes represent a promising class of theranostic materials that integrate coordination chemistry, redox biology, cancer therapy, and molecular imaging. The reviewed studies demonstrate that coordination parameters including ligand structure, Fe oxidation state, stoichiometry, and supramolecular organization regulate iron availability, therapeutic activation, and imaging behavior. These platforms show potential for ferroptosis, chemodynamic therapy, photothermal treatment, immune modulation, and gadolinium-free MRI applications. Despite these advances, clinical translation requires overcoming challenges related to structural heterogeneity, reproducibility, serum stability, biodistribution, long-term iron handling, and regulatory standardization. Future efforts should focus on chemically defined architecture, quality-by-design manufacturing, and comprehensive preclinical safety assessment. Addressing these challenges will be essential for converting iron-polyphenol systems from promising experimental platforms into clinically relevant cancer theranostic technologies.

Future directions

Future development of iron-polyphenol theranostic systems requires a shift toward chemically defined and clinically translatable platforms. Priority should be given to the rational design of well-controlled Fe-polyphenol architectures, including direct comparison of Fe(II)- and Fe(III)-based systems under standardized conditions and clarification of the individual contributions of iron, polyphenolic ligands, and incorporated therapeutic components. Comprehensive biological evaluation should include serum/plasma stability, competing-ligand interactions, pharmacokinetics, organ biodistribution, and repeated-dose toxicity studies rather than relying only on short-term cytotoxicity assays. In parallel, MRI studies should adopt standardized reporting protocols considering magnetic field strength, temperature, pH, and measurement environment to enable meaningful comparison between platforms. Finally, successful clinical translation will require scalable manufacturing strategies, defined quality-control parameters, validation in clinically relevant tumor models, and comparison with established therapeutic and imaging standards to establish the true clinical value of iron-polyphenol theranostics.

Ethical approval

Not applicable. This is a review article that does not involve original research on human participants, animal subjects, or personal data requiring ethical approval.

Declaration of generative AI and AI assisted technologies

During the preparation of this manuscript, the authors used ChatGPT (GPT-5.6; OpenAI, San Francisco, CA, USA) for language refinement, generation of the graphical abstract, and technical enhancement of figure resolution. Resolution enhancement was limited to improving visual quality and did not add, remove, or modify any scientific features or data. AI tools were not used to generate scientific data, analyze or interpret results, or draw scientific conclusions. The authors reviewed and verified all AI-assisted textual and visual materials and take full responsibility for the accuracy, originality, and integrity of the published content.

Funding

This review received no specific grant from any funding agency in the public, commercial, or not for profit sectors.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRedit authorship contribution statement

Waqas Ihsan: investigation, writing-original draft, review and editing; **Jiraporn Kantapan:** conceptualization, investigation, write-review and editing, visualization; **Nathupakorn Dechsupa:** conceptualization, supervision, writing-review and editing, project administration.

Acknowledgment

The author gratefully acknowledges the support of the Chiang Mai University Presidential Scholarship and the Department of Radiologic Technology, Faculty of Associated Medical Sciences, Chiang Mai University, Thailand.

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